Original Article

Refractory Angina Frequencies during 7 weeks Treatment by Enhanced External Counterpulsation in Coronary Artery Disease Patients with and without Diabetes

Abstract

Background: Refractory angina is a clinical diagnosis which implies to chronic pain due to coronary artery insufficiency and it is often resistant to routine cardiac treatment. The present study conducted to compare changes in refractory angina frequencies during 7 weeks treatment by enhanced external counterpulsation (EECP) in coronary artery disease (CAD) patients with and without diabetes. **Methods:** In this retrospective study, 94 CAD patients (30 diabetics vs. 64 nondiabetics) who referred to cardiac rehabilitation department of Imam Ali Hospital of Kermanshah, Iran, during January 2006–2014 were assessed. The interventional method was EECP and medical records and frequencies of self-reported chest pain were research instruments. Data were analyzed through Chi-square test, mixed repeated measures, and Bonferroni test. **Results:** Frequencies of pain in both diabetic and nondiabetic groups during 7 weeks had linear reduction, but this reduction was significant only among nondiabetic patients ($P < 0.0005$). Furthermore, the significant reduction in frequencies of pain among this group begins after the 5th week. **Discussion:** Diabetes is one of the obstacles to the successful control of pain frequencies by the EECP in patients with CAD. Future studies may pay attention to the confounding role of diabetes in improving the severity of chest pain.

Keywords: *Angina, chest pain, chronic disease, coronary artery disease, diabetes, enhanced external counter pulsation*

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Introduction

Refractory angina is a clinical diagnosis which implies chronic pain due to coronary artery stenosis and it is often resistant to routine cardiac treatment.[1] The severity of pain in patients with refractory angina is in third or fourth level according to the classification of Canada Cardiovascular Society (CCS) which chest pain or discomfort occurs even in mild activity or rest time.[2] This disease is concerned as a horror and disabling condition that its management is a very difficult problem. Most individuals who suffer from refractory angina do not find appropriate relief for their pain and they refer to emergency departments of hospitals and treatment centers frequently to seek medical help and they usually undergone repeated cardiac assessments. The probable cause of this condition may be the anatomy of the coronary artery which inhibits revascularization.[3]

The prevalence of angina pectoris has been increased among men and women with increasing age and it is estimated that 2%–4% of European adult population is affected by angina.[4] In the other hand, more than 15% of patients with cardiac angina have criteria for refractory angina that they must necessarily be treated.[1] The interventions of this field include a wide range of methods such as routine treatments as medicines and invasive interventions such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention.[5] Despite these treatments, mean of treatment success in patients with systematic severe chest pain has increased. While refractory angina is concerned as a noticeable clinical problem, and recently, it is associated with the search for alternative treatments. One of these methods is enhanced external counterpulsation (EECP) which its role in angina treatment has not been well identified.[6]

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EECP is one of the most hopeful treatments for relief of angina.[1] EECP is a nonpharmacological/noninvasive treatment which is used for when that routine treatments are not applicable.[7,8] Different studies suggest the efficacy of EECP in the reduction of the severity and frequencies of refractory angina.[9-11] Nichols *et al*.[12] found that EECP is effective in reducing pain severity and frequencies based on CCS class. Another study[13] indicates that EECP significantly reduced severity of angina based on CCS class in nonappropriate patients for invasive interventions. In addition, EECP is significantly effective in quality of life, the severity of ischemia in myocardial perfusion, left ventricular end-systolic and end-diastolic diameter, and time duration of exercise test.[13] Moloodi *et al*. (2012) after studying 30 patients with heart failure found that EECP is significantly effective in the improvement of left ventricle ejection fraction, wall-motion abnormalities, the change percentage of left ventricular diameter, and an internal diameter of the left ventricle in end of systole. In addition, the results indicated that this treatment is effective in reduction of frequencies of angina and improvement of functional level in patients.[8]

Although most of the studies have indicated the efficacy of EECP in the reduction of severity and frequencies of pain, it seems that some associated conditions such as diabetes can impact on its efficacy. Diabetes can increase the risk of cardiovascular diseases (CVDs) through dyslipidemia, increased triglycerides (TG), and low-density lipoprotein (LDL), decreased high-density lipoprotein (HDL), and increased ratio of total cholesterol versus HDL. Indeed, diabetes has a significant role in obesity and overweight as one of the risk factors of CVDs[14] and it is probable that it impacts on treatment process by EECP. Although previous findings in this field have controversies, some studies indicate that EECP can improve the function of peripheral vessels, biochemical measurements, and glucose tolerance in patients with abnormalities of glucose tolerance significantly[15] and subsequently pain severity decreases in more than two-thirds of diabetic patients.[16] Conversely, Lawson *et al*.[17] showed that EECP has not marked effect on reduction of angina severity in diabetic patients.

The mentioned studies just considered the severity of pain. The studies ignored frequencies of pain and the linear pattern of pain reduction during 7 weeks treatment by EECP. We intended compare the changes in each week with the past weeks in a format of the linear process. If the pain frequencies decrease in each week compare to the past week it means that there is the linear reduction but if the frequencies have in irregular process or they have zigzag swing and they decrease or increase during weeks the process is not linear. Thus, we aimed to compare pain frequencies during 7 weeks treatment and in the presence of positive change, assess the beginning time of efficacy exactly. Given that the previous studies did not investigate the confounding role of diabetes, we aim to study the change process of pain frequencies separately. Hence, the present study aimed to compare the changes in angina frequencies during 7 weeks treatment by EECP in coronary artery disease (CAD) patients with diabetes and without diabetes.

Methods

This retrospective study was approved by the Ethical Committee of the Kermanshah University of Medical Sciences (KUMS.REC.1394.303). The statistical community concluded all of CAD patients with a diagnosis of a cardiologist who referred during 2006–2014 for EECP treatment to cardiac rehabilitation (CR) center of Imam Ali hospital of Kermanshah city, Iran. Most of these patients were visited by the cardiologists of the center and passed primary assessments, and finally, they referred for EECP treatment. Inclusion criteria concluded perfect medical record, diagnosis of the CAD, and do not use anti-angina pills during treatment. A total number of cases were 118 that after entering inclusion criteria 94 patients remained as main cases. Data were analyzed after recording information in special forms which made by the research team and after control of statistical presumptions.[18] Demographic and medical data related to EECP patients were recorded in SPSS-20 (IBM Corp. Armonk, NY, USA) software application.

Enhanced external counterpulsation intervention

EECP system totally concluded of three pairs of cuffs and monitoring system. It acts as cuffs are closed to the lower limb and they inflate from distal to proximal and exert pressure to vessels of the lower limb.[19] According to electrocardiogram waves in EECP treatment, pressure entered to the lower limb from leg to buttock during diastole and suddenly pressure relieved at beginning of systole. Pressure changes performed through air cuffs which closed to lower limb and inflate and deflate during each cardiac cycle. During increased pressure on lower limb in diastole phase, venous return and coronary flow are increased and during sudden decreased pressure in systole phase, after load decreases. This acts same as intra-aortic balloon pump and induces hemodynamic changes and increases venous return.[8] This treatment is conducted under physician direct supervision during 7 weeks (5 times/week) in 35 1-h sessions.

Instruments

Patients' medical records

The executive data were obtained from the data bank of CR department of Imam Ali hospital of Kermanshah. This data bank includes information related to patients with chronic CVDs, especially chronic heart failure and refractory angina who referred to EECP treatment. Based on EECP protocol, the mentioned treatment was conducting

during 7 weeks and 35 sessions (5 sessions/week). At first, the patients demographic and medical data were recorded exactly and information related to pain frequencies were asked in the interval between sessions. The presence of a diabetic or nondiabetic condition is identified through medical records.

Angina frequencies

These frequencies identified as high prevalence of chest pain due to decreased coronary blood supply or increased myocardial need to oxygen.[20] The score of self-reported pain frequencies (daily registration) was the scale to measure angina. According to the classification of CCS, the patients were asked to record any chest pain experienced in Grade II to IV.

Data analysis

Data analysis conducted through SPSS 20 and descriptive statistics (mean, standard deviation, and percent), Chi-square, and analysis of variance (ANOVA) by mixed repeated measures.[18] This method used because patients were assessed in 7 separated weeks to indicate the linear process of treatment exactly. In addition because of separated assessment of two diabetic and nondiabetic groups in 7 weeks, Bonferroni test was used to compare the significance of dependent variable between two groups.

Results

The findings related to 94 patients (74 men and 20 women) with the mean age of 58.1 ± 10.6 years were analyzed. The clinical and behavioral variables with changes in their medicines during treatment were shown separately in Table 1. As seen in this table, there are significant differences between two groups only in smoking and history of CABG as smoking and open cardiac surgery are more in nondiabetic patients. There are no significant differences in the other variables between groups.

Table 2 indicates the scores of self-report of pain frequencies during 7 weeks of EECP treatment. Furthermore, the results of MANOVA indicates that F is not significant to interact of group × pain frequencies (F [6, 87] =1.506; $P = 0.186$). Hence, there is not a significant difference between diabetic and nondiabetic patients in the linear process of pain frequencies during 7 weeks. In addition, based on results of Grace House Gizer related to intersample effects (F [4.69, 276.46] =1.270; $P = 0.277$) indicated that there are parallel slopes regressions of pain frequencies between two groups in 7 weeks.

The results of Table 3 show the changes of scores in different levels of the dependent variable in the separation of the group. Based on these results, it can be suggested that pain frequencies have the linear reduction in two groups during 7 weeks and this reduction is significant at least in one group (F [1, 92] =34.405; $P < 0.0005$).

Table 1: Comparison of clinical and behavioral variables and drug changes during the course of treatment

Variables	Diabetic patients, *n* (%)	Nondiabetic patients, *n* (%)	*P*[a]
Diagnosis			
Chronic heart failure	19 (63.3)	47 (73.4)	0.318
Refractory angina	11 (36.7)	17 (26.6)	
MI history	21 (70)	38 (59.4)	0.321
CABG history	8 (26.7)	34 (53.1)	0.016
Hypertension history	10 (33.3)	20 (31.2)	0.840
Hyperlipidemia history	15 (50.0)	29 (45.3)	0.671
Heart drug changes	4 (13.3)	10 (15.6)	0.771
Alcohol abuse	1 (3.3)	5 (7.8)	0.408
Drug abuse	7 (23.3)	12 (18.7)	0.606
Smoking	8 (26.7)	41 (64.1)	0.001

[a]The statistical significant is based on Chi-square test.
MI: Myocardial infarction, CABG: Coronary artery bypass grafting

Table 2: The mean and standard deviation of pain periods (frequency of pain events per week) during treatment divided by group

Variable[a] (weeks)	Diabetic (*n*=30)	Nondiabetic (*n*=64)	Total (*n*=94)
1	0.77±1.36	0.81±1.22	0.80±1.26
2	0.73±1.36	0.92±1.36	0.86±1.36
3	0.60±1.19	0.86±1.40	0.78±1.34
4	0.33±0.71	0.66±1.25	0.55±1.11
5	0.33±0.92	0.61±1.08	0.52±1.03
6	0.43±0.86	0.28±0.70	0.33±0.75
7	0.27±0.64	0.25±0.69	0.25±0.67

[a]The scores are based on mean±SD. SD: Standard deviation

Table 3: The repeated-measure model of the subjects in terms of frequencies of pain events per week

Source	Test	*F*	*P*
Dependent variable	Linear[a]	34.405	0.0005*
	Quadratic[b]	0.221	0.640
	Cubic[c]	0.933	0.337
	Order 4	1.163	0.284
	Order 5	0.006	0.937
	Order 6	1.307	0.256

[a]Liner changes in frequency of pain; [b]Quadratic changes in frequency of pain; [c]Nonliner changes in frequency of pain, *The frequency of pain follows a declining linear process: $P<0.0005$

The results of between-subjects comparison on dependent variable levels through Bonferroni test in diabetic and nondiabetic patients are shown in Table 4. Based on the results, EECP treatment can decrease pain frequencies during 7 weeks in nondiabetic patients significantly compared to diabetic patients. Indeed, there is not the difference in pain frequencies between none of the weeks in the diabetic group while there is a significant difference between 5 first weeks with 2 final weeks in nondiabetic patients ($P < 0.05$). In addition, the results of

Table 4: The results of analysis of variance (Bonferroni *post hoc* test) to compare of frequencies of pain events per week between the groups

Week	Total	Nondiabetic		Diabetic	
	Mean±SD	Mean±SD	*F*	Mean±SD	*F*
1	0.80±1.26	0.81±1.22	-	0.77±1.36	-
2	0.86±1.36	0.92±1.36	−0.11	0.73±1.36	0.03
3	0.78±1.34	0.86±1.40	−0.05	0.60±1.19	0.17
4	0.55±1.11	0.66±1.25	0.16	0.33±0.71	0.43
5	0.52±1.03	0.61±1.08	0.20	0.33±0.92	0.43
6	0.33±0.75	0.28±0.70	**0.53**	0.43±0.86	0.33
7	0.25±0.67	0.25±0.69	**0.56**	0.27±0.64	0.50
2	0.86±1.36	0.92±1.36	-	0.73±1.36	-
3	0.78±1.34	0.86±1.40	0.06	0.60±1.19	0.13
4	0.55±1.11	0.66±1.25	0.27	0.33±0.71	0.40
5	0.52±1.03	0.61±1.08	0.31	0.33±0.92	0.40
6	0.33±0.75	0.28±0.70	**0.64**	0.43±0.86	0.30
7	0.25±0.67	0.25±0.69	**0.67**	0.27±0.64	0.47
3	0.78±1.34	0.86±1.40	-	0.60±1.19	-
4	0.55±1.11	0.66±1.25	0.20	0.33±0.71	0.27
5	0.52±1.03	0.61±1.08	0.25	0.33±0.92	0.27
6	0.33±0.75	0.28±0.70	**0.58**	0.43±0.86	0.17
7	0.25±0.67	0.25±0.69	**0.61**	0.27±0.64	0.33
4	0.55±1.11	0.66±1.25	-	0.33±0.71	-
5	0.52±1.03	0.61±1.08	−0.05	0.33±0.92	0.00
6	0.33±0.75	0.28±0.70	**0.37**	0.43±0.86	−0.10
7	0.25±0.67	0.25±0.69	**0.41**	0.27±0.64	0.07
5	0.52±1.03	0.61±1.08	-	0.33±0.92	-
6	0.33±0.75	0.28±0.70	0.33	0.43±0.86	−0.10
7	0.25±0.67	0.25±0.69	**0.36**	0.27±0.64	0.07
6	0.33±0.75	0.28±0.70	-	0.43±0.86	-
7	0.25±0.67	0.25±0.69	0.03	0.27±0.64	0.17

Boldface indicates statistically significant (P<0.05). SD: Standard deviation

Figure 1 indicate that significant reduction process in pain frequencies begins after 5th week in nondiabetic patients.

Discussion

The present study aimed to compare the changes in angina frequencies during 7 weeks treatment by EECP in CAD patients with and without diabetes. In line with the past studies,[12,15,16] the findings of the present study indicate that pain frequencies have the linear reduction in both groups during 7 weeks. Although EECP treatment can reduce pain frequencies in nondiabetic patients significantly compared to diabetic patients. Furthermore, it has been indicated that reduction in pain frequencies mainly begins after 5th week in nondiabetic group.

Comorbid diseases in CAD patients with refractory angina such as diabetes can impact on the efficacy of EECP. Diabetes can increase the risk of CVDs through dyslipidemia, increased TG and LDL, decreased HDL, and increased ration of total cholesterol to HDL. Indeed, diabetes has a significant role in obesity and overweight as

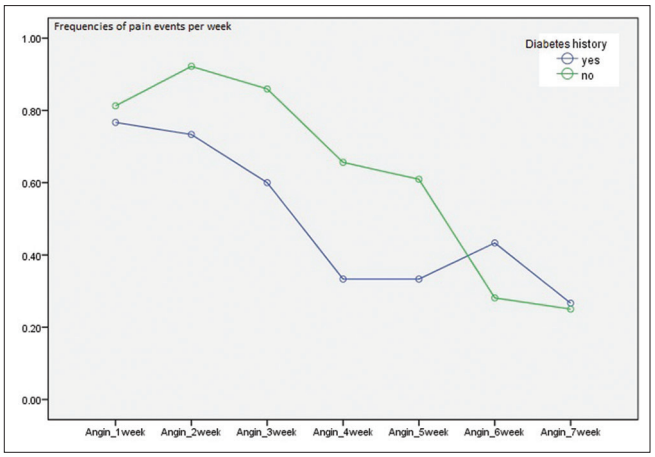

Figure 1: Comparison of pain frequencies during treatment sessions divided by group

one of the risk factors of CVDs,[14] and it is probable that it impacts on treatment process by EECP. Of course, the past findings in this field have controversies while the results of two studies indicate that EECP can improve function of peripheral vessels, biochemical measurements, and glucose tolerance in patients with abnormalities of glucose tolerance significantly,[15] and subsequently, pain severity decreases in more than two-thirds of diabetic patients after treatment significantly.[16]

In consistent with the results of Lawson *et al*.[17] that indicate EECP has not marked effect on reduction of angina severity in diabetic patients, we found that EECP has no significant effect in reducing pain frequency among CAD patients with diabetes. A careful look at changes in pain frequency in the groups shows that both groups have relatively similar changes (−0.50 for diabetics vs. −0.56 for nondiabetics). This difference is likely to result from the heterogeneity of the sample size of the two groups. In fact, the larger sample size in the nondiabetic group has resulted in significant results.

In general, it is obvious that plaque wound and intravessels clots in diabetic patients are significantly more than others and it correlates with angina in patients with the acute coronary syndrome.[21] EECP treatment can improve significantly the function of peripheral vessels, biochemical measures, and glucose tolerance, and subsequently, reduces the severity of patients pain significantly.[15,16] EECP treatment can improve endothelial function and it leads to increased use of insulin. In addition, EECP treatment increases the density of microcirculation and presence of transmitter protein of glucose 4 (GLUT4) in the skeletal muscles.[15] Hence, this treatment through different mechanisms can lead to decreased angina frequencies. Although it seems that improvement level and reduction in angina frequencies are more marked in nondiabetic patients compared to diabetic patients.

Limitations

Lack of an equal number of two groups and fewer diabetic patients was one of the limitations of this study. Although we

concluded that reduction process of pain in diabetic patients was not significant compared to nondiabetic patients, this issue may be due to fewer diabetic patients compared to another group. Hence, it recommended that larger sample size of diabetic patients will be evaluated in the future studies to evaluate the accuracy of these findings again. This research is a retrospective study and pain is very subjective measuring. The current study can be repeated with a cross-sectional design. In future studies, using standard questionnaires to measure the frequency and severity of pain can be beneficial. In addition, examination of patients from all over the country can increase the generalizability of the results.

Conclusion

The present study aimed to compare the changes in angina frequencies during 7 weeks treatment by EECP in CAD patients with and without diabetes. The findings of the present study indicate that pain frequencies have the linear reduction in both groups during 7 weeks. Although EECP treatment can reduce pain frequencies in nondiabetic patients significantly compared to diabetic patients. This difference is likely to result from the heterogeneity of the sample size of the two groups. In addition, it has been indicated that reduction of pain frequencies significantly begins after 5th week in nondiabetic group. It seems that diabetes as one of the comorbidities with CAD is concerned as a barrier for EECP success in reduction of experienced pain frequencies and more studies in this field are recommended.

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Conflicts of interest

There are no conflicts of interest.

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